

THE UTILIZATION OF INTRAVENOUSLY ADMINISTERED  
GLUCOSE, FRUCTOSE, AND INVERT SUGAR IN CATTLE

by

DENNIS DONALD GOETSCH

B. S., Kansas State College  
of Agriculture and Applied Science, 1952  
D. V. M., Kansas State College  
of Agriculture and Applied Science, 1952

A THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Physiology

KANSAS STATE COLLEGE  
OF AGRICULTURE AND APPLIED SCIENCE

1955



LD  
2668  
T4  
1955  
G64  
c.2  
Documents.

11

TABLE OF CONTENTS

|  |    |
|--|----|
| INTRODUCTION . . . . .   | 1  |
| REVIEW OF LITERATURE . . . . .                                   | 2  |
| Fructose and Invert Sugar . . . . .                              | 2  |
| Metabolic Pathways of Carbohydrates, Fats and Proteins . . . . . | 9  |
| Carbohydrate Metabolism . . . . .                                | 9  |
| Fat Metabolism . . . . .   | 9  |
| Protein Metabolism . . . . .                                     | 11 |
| Ruminant Nutrition and Ketosis . . . . .                         | 11 |
| MATERIALS AND METHODS . . . . .                                  | 14 |
| RESULTS AND DISCUSSION . . . . .                                 | 16 |
| Blood Analysis . . . . .   | 16 |
| Urine Analysis . . . . .   | 26 |
| SUMMARY AND CONCLUSIONS. . . . .                                 | 43 |
| ACKNOWLEDGMENT . . . . .   | 45 |
| REFERENCES . . . . .   | 46 |

## LIST OF TABLES

| Table<br>Number: |   | Page: |
|------------------|---|-------|
| 1                | Blood sugar determinations in 12 calves following intravenous infusion of glucose . . . . .   | 19    |
| 2                | Blood sugar determinations in 12 calves following intravenous infusion of fructose . . . . .  | 21    |
| 3                | Blood fructose determinations in 12 calves following intravenous infusion of fructose . . . . .   | 22    |
| 4                | Blood sugar determinations in 12 calves following intravenous infusion of invert sugar . . . . .  | 23    |
| 5                | Blood fructose determinations in 12 calves following intravenous infusion of invert sugar . . . . .   | 25    |
| 6                | Average total blood sugar values and standard deviations in 12 cattle before and after intravenous infusions of glucose, fructose, and invert sugar . . . . . | 30    |
| 7                | Average blood fructose values and standard deviations in 12 cattle before and after intravenous infusions of fructose and invert sugar . . . . .              | 31    |
| 8                | Urinary sugar excretions in six hours following intravenous infusion of glucose . . . . .   | 32    |
| 9                | Urinary sugar excretions in six hours following intravenous infusion of fructose . . . . .  | 33    |
| 10               | Urinary sugar excretions in six hours following intravenous infusion of invert sugar . . . . .  | 34    |
| 11               | Average urinary sugar excretions and standard deviations of five cattle following intravenous infusions of glucose, fructose, and invert sugar . . . . .      | 35    |
| 12               | Average urinary sugar at periodic intervals before and after intravenous infusions of glucose, fructose, and invert sugar . . . . .                           | 40    |
| 13               | Average urinary fructose at periodic intervals before and after intravenous infusions of fructose and invert sugar . . . . .                                  | 40    |

## LIST OF FIGURES

| Figure<br>Number: |   | Page: |
|-------------------|---|-------|
| 1                 | The central place of acetyl-Co A in intermediary metabolism . . . . .   | 10    |
| 2                 | Calibration curve used for the calculation of glucose values . . . . .  | 17    |
| 3                 | Calibration curve used for the calculation of fructose values . . . . .   | 18    |
| 4                 | Average blood sugar values of 12 calves following intravenous infusions of glucose, fructose, and invert sugar . . . . .  | 27    |
| 5                 | Average blood fructose values of blood samples taken prior to and following intravenous infusions of fructose and invert sugar . . . . .                                  | 28    |
| 6                 | Typical post-injection blood sugar values as shown by calf 35 following intravenous infusions of glucose, fructose, and invert sugar . . . . .                            | 29    |
| 7                 | Average urinary glucose eliminated by five calves in six hours following intravenous infusions of glucose, fructose, and invert sugar . . . . .                           | 36    |
| 8                 | Average urinary fructose eliminated by five calves following intravenous infusions of fructose and invert sugar . . . . .   | 37    |
| 9                 | Average urinary sugar eliminated by five calves in six hours following intravenous infusions of glucose, fructose, and invert sugar . . . . .                             | 38    |
| 10                | Average urinary glucose, fructose and total sugar eliminated by five calves in six hours following intravenous infusions of glucose, fructose, and invert sugar . . . . . | 39    |
| 11                | Average total sugar values of urine samples taken at periodic intervals following intravenous infusions of glucose, fructose, and invert sugar . . . . .                  | 41    |
| 12                | Average fructose values of urine samples taken at periodic intervals following intravenous infusions of fructose and invert sugar . . . . .                               | 42    |

## INTRODUCTION

The demonstration that insulin affected phosphorylation of glucose and that specific hexokinases for fructose and glucose existed in the liver led to investigations with fructose as a therapeutic agent in diabetes mellitus and other disturbances of carbohydrate metabolism. Later studies indicated separate metabolic pathways for glucose and fructose and that fructose metabolism was not affected in diabetes. Further investigations showed that the utilization of fructose was not dependent on insulin in normal dogs and that fructose was more easily phosphorylated than glucose. Other workers have demonstrated less urinary loss from intravenously administered fructose and invert sugar as compared with glucose. Direct assimilation of fructose by peripheral tissues has likewise been demonstrated. When normal dogs were compared with dogs made acidotic with ammonium chloride it was found that the rate of disappearance of glucose from the blood was slower in the acidotic animal than in the normal individual, indicating that acidosis inhibited cellular uptake of glucose and/or processes of phosphorylation. Recent work has shown fructose to be ketolytic in depancreatized ketotic dogs. These findings suggested a need for an evaluation of the utilization of fructose and invert sugar in cattle since it is well known that ruminants differ markedly in their carbohydrate metabolism from that of monogastric animals. Further, in case of greater advantages of these sugars over glucose, their superiority as valuable therapeutic agents would be indicated in the

many disturbances of the ruminant where therapy with glucose is employed and especially in ketosis of dairy cattle.

## REVIEW OF LITERATURE

### Fructose and Invert Sugar

The use of fructose in carbohydrate therapy was first suggested by Minkowski (47) in 1893. This worker, using dogs made diabetic by extirpation of the pancreas, showed that fructose was better tolerated in these experimental animals than glucose. Cori (12), studying the rate of glycogen formation in the liver of normal and insulinized rats during the absorption of glucose, fructose, and galactose, found that glucose and fructose are on a par as glycogen formers even though glucose was absorbed twice as fast as fructose. It was further shown that large doses of insulin almost completely suppressed the glycogen formation in the liver from glucose and from fructose. Wierzuchowski (78), using normal dogs, found higher blood sugar values following intravenous infusion of glucose when compared to fructose infusion. Employing these same experimental animals it was shown further that insulin had no effect on fructose utilization whereas glucose excretion dropped from 10 per cent to 1 per cent following insulin injection. Similar findings in rats were reported by Cori and Cori (13). These workers, however, found fructose less readily retained by the kidneys when compared to glucose. They likewise reported that insulin had no effect on fructose



utilization whereas large doses of insulin raised the intravenous glucose tolerance about 20 per cent. Davidson et al. (15), injecting fructose intravenously into rabbits previously infused with glucose, found a more rapid fall in blood glucose as compared to glucose injection. They concluded that fructose stimulated the production of insulin. Insulin, on the other hand, had no effect on the rate of disappearance of blood fructose. Using rat liver slices and homogenates in the presence of adenosine triphosphate (ATP),  $MgCl_2$ , ketoglutarate, and a phosphate buffer, Vestling et al. (74) demonstrated that fructose phosphorylation occurred ten times more readily than glucose phosphorylation in vitro. Weinstein (76, 77) showed that when an invert sugar solution containing equal quantities of glucose and fructose was injected into human subjects less glycosuria was produced than when glucose was employed alone.

The comparative utilization of fructose and glucose given intravenously has been investigated by Weichselbaum et al. (75). In ten experiments on normal human subjects comparative intravenous injections of 10 per cent glucose and 10 per cent fructose were carried out. Even at rapid rates of infusion very little fructose appeared in the urine as compared to the amount of glucose. Diuresis was also less pronounced with fructose. Moreover, the fructose infusions were not followed by either hyperglycemia nor by an excessive rise in the blood fructose level, thus indicating a more rapid utilization of fructose and presumably more rapid glycogenesis. Conversely, this investigator demonstrated that continuous intravenous alimentation with glucose

stimulated the pancreas to produce increased amounts of insulin and thus led to hypoglycemia following intravenous injection.

Brady and Gurin (5) showed that liver slices from normal rats and cats readily converted  $C^{14}$  labeled acetate to long chain fatty acids. However, liver slices of alloxanized rats and pancreatectomized cats are relatively incapable of carrying out this process. The addition of insulin, glucose, fructose-6-phosphate, oxalacetate, or ketoglutarate to the incubating medium failed to re-establish fatty acid synthesis in liver slices from these animals. Similar experiments using alloxan diabetic rats have shown a reduction in the capacity of liver slices from these animals to convert glucose, fructose, acetate, lactate, and pyruvate to fatty acids (8, 10, 11, 23, 52). However, other investigators (9) using similar experimental animals and conditions demonstrated a restoration of the ability of the previously insulin treated liver slices to convert  $C^{14}$  glucose to fatty acids as well as oxidize it to carbon dioxide. The ability of insulin treated, alloxan diabetic livers to convert  $C^{14}$  labeled acetate and formate to fatty acids has likewise been demonstrated (23). Chernick and Chaikoff (8), once more using  $C^{14}$  labeled glucose, fructose, and acetate and employing liver slices from normal and alloxan diabetic rats, found the conversion of glucose to both carbon dioxide and fatty acids to be markedly depressed in the diabetic liver. On the other hand, the oxidation of fructose and acetate to carbon dioxide proceeded at normal rates in the diabetic liver although its conversion to fatty acids was impaired. Thus defective lipogenesis in the diabetic



liver can be repaired in two ways, viz., by insulin injections or by fructose feeding. However, the actions of the two treatments upon lipogenesis are not identical. The hormone repairs lipogenesis not only from acetate, lactate, and pyruvate, but also from glucose (9). Fructose feeding, on the other hand, repairs lipogenesis from the two-carbon intermediate but not from glucose (1). This difference indicated that the feeding of fructose by circumventing the initial block in glucose utilization provided a continuous source of substrates in the glycolytic system. This demonstrated that an active glycolytic system is required for maintenance of lipogenesis in the liver. Support for such a view is found in the rapid decrease in lipogenesis from glucose and acetate that occurs in the fasted rat and in the rat fed a diet totally devoid of carbohydrate (5).

Wyshak and Chaikoff (82) compared the relative abilities of liver slices from normal and fasted rats to metabolize radioactive glucose and fructose since glucose utilization is temporarily inhibited following a prolonged fast (7). It was learned that the abilities of livers from rats fasted 72 hours to convert glucose to carbon dioxide decreased by about 50 per cent; however, livers from rats fasted under similar conditions showed no significant difference in their abilities to oxidize fructose.

Early studies on the renal threshold of fructose in man found it less readily retained by the kidneys when compared to glucose (81). Other investigators (46, 67) found that similar amounts of glucose and fructose (less than 10 per cent) appeared in the urine following the infusion of these two sugars in normal

human subjects. Weinstein (76, 77), using normal human beings, reported that invert sugar solutions are retained more readily in the body than either fructose or glucose. Frost et al. (24), comparing the tolerance of rapidly injected glucose and invert sugar in normal ambulatory young men, demonstrated less urinary loss of reducing substances following invert sugar infusions. Rice and Strickland (56) reported that invert sugar produced less hyperglycemia and less glycosuria in surgical patients than when glucose was used as the source of carbohydrates. However, Smith et al. (68) failed to disclose any advantage of invert sugar over glucose with regard to renal tolerance. Moncrief et al. (48) in one series of observations in humans compared fructose and glucose on alternate days in the same patient after surgical operation. Under these conditions, total 24 hour urine specimens showed an average loss of 25.3 gm of reducing sugars on the days when glucose was infused as compared with a loss of 9.9 gm when fructose was administered.

Five diabetic and three normal human subjects were used by Miller et al. (46) to compare the utilization of fructose and glucose. In normal subjects fructose produced a much greater rise in blood pyruvic acid and a rise rather than a fall in plasma citrate as compared to glucose. Fructose also disappeared more rapidly from the blood stream. In diabetic subjects, in the absence of insulin, fructose produced the same rise in pyruvic acid as was found in normal subjects, while glucose produced either a slight or delayed rise. Increases in plasma citric acid after fructose administration were similar to those in

normal individuals. The blood fructose disappearance curve and the amount of fructose excreted in the urine in patients with diabetes were the same as in normal subjects. Fructose invariably produced a fall in serum inorganic phosphate, while a fall did not usually occur after glucose. These studies indicated that the metabolism of fructose differs from that of glucose in both the normal and diabetic subject and that the metabolism of fructose in the diabetic individual is similar to that in the normal even in the absence of insulin.

In further detailed studies on the administration of fructose solutions to patients with diabetes, Smith et al. (67) found the impairment of fructose tolerance in such patients was relatively small and not at all comparable to impairment in tolerance of the same patients to glucose. When amounts of serum inorganic phosphate following glucose and fructose administration were compared, it was noted that the phosphate levels fell more rapidly after fructose administration and also returned more rapidly to normal. Much higher levels of such carbohydrate intermediates as pyruvate, lactate, and alpha-ketoglutarate were found in the blood following fructose injection. These observations are consistent with the theory that the phosphorylation of glucose to glucose-6-phosphate is impaired in diabetes, while the phosphorylation of fructose, which is uninfluenced by insulin, proceeds at a normal rate.

Van Itallie et al. (73), in further studies on fructose utilization, measured the peripheral fructose differences in arterial and venous blood. In this study ten human subjects

receiving a constant intravenous infusion of ten per cent fructose, following an initial priming injection, were employed. Maintenance of consistent and appreciable arteriovenous differences under these circumstances occurred in every case thus indicating direct assimilation of fructose by peripheral tissues.

Mackler et al., using dogs made acidotic by hepatectomy (41) or by the injection of ammonium chloride (40), found the disappearance of glucose from the blood was slower in acidotic than in non-acidotic states. This investigation indicated that acidosis inhibits the cellular uptake of sugar by interfering with the production of insulin and/or with the action of insulin in bringing about processes of phosphorylation.

The comparative effects of intravenously administered glucose, glucose plus insulin, and fructose on the concentrations of ketone bodies in the blood and their excretion in the urine of dogs were studied by Whittlesey and Zubrod (79). The experimental animals were totally depancreatized and deprived of exogenous insulin for periods of four to ten days. The effect observed following fructose administration was similar to that seen with the infusion of glucose plus exogenous insulin, viz., a fall in the blood concentration of ketone bodies. This fall was not the result of urinary excretion of ketone bodies. Glucose infusion alone was accompanied by a continued rise in ketone body concentration in the blood. This indicated that fructose in the absence of insulin is ketolytic when administered to depancreatized, ketotic dogs.

## Metabolic Pathways of Carbohydrates, Fats, and Proteins

During recent years significant advances have been made in the understanding of intermediary metabolism. With this advancement has come an increase in the knowledge of the various pathways by which the major metabolites--carbohydrates, fats, and proteins--are utilized by the animal body. Recent reviews on fat metabolism by Lehninger (36) and Lipmann (38) have indicated the central role of coenzyme A (CoA) in the intermediary metabolism of these metabolites (Fig. 1).

Carbohydrate Metabolism. The anaërobic pathway of glucose metabolism has been known for some time. Upon absorption, glucose may be stored as glycogen or if needed for energy may be phosphorylated and broken down to pyruvate. Pyruvic acid may be further oxidatively decarboxylated to form carbon dioxide and acetate or it may be carboxylated to form oxalacetate (39, 50, 51). If decarboxylation occurs, the acetate then may combine with CoA to form acetyl CoA and thus enter the tricarboxylic acid energy cycle.

Fat Metabolism. In the utilization of fats, it is first necessary that they be hydrolyzed to fatty acids and glycerol. In order for fatty acid oxidation to proceed it is necessary that the oxidation of tricarboxylic acid cycle intermediates be proceeding normally so that a continuous supply of ATP may be available as a source of high energy bonds (14). Lehninger (36), Lipmann (38), and Green (25) have described the process of fatty acid oxidation as being one in which the fatty acid molecule



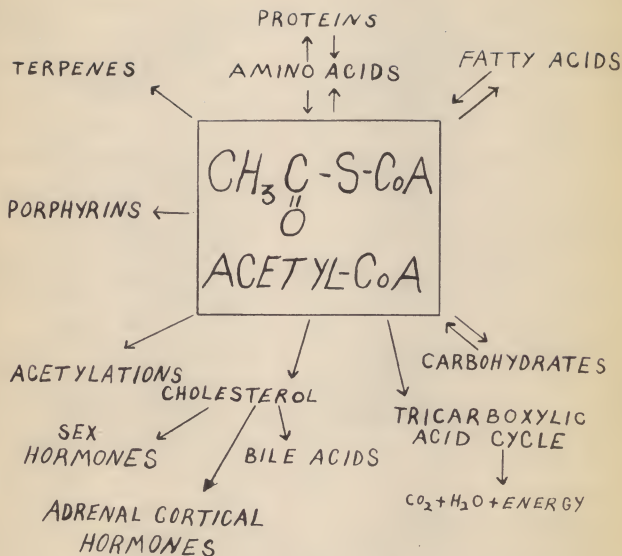


FIG. 1. The central place of acetyl-CoA in intermediary metabolism.



forms a complex with CoA. The CoA-fatty acid complex then undergoes beta oxidation in which a two-carbon unit is split off and which combines with another CoA molecule to form acetyl CoA. The acyl CoA residue again undergoes successive beta oxidation until the acid has been degraded to an acetoacetyl CoA fragment. This last  $C_4$  fragment may be degraded further to acetyl CoA or it may be hydrolyzed to free acetoacetic acid (4). Acetoacetic acid may be metabolized after once more combining with CoA or it may be decarboxylated to acetone. Normally the latter pathway appears to be followed only to a minor degree (4). The glycerol portion of the fat molecule is oxidized to triose phosphate and may then form pyruvic acid (17, 18). Acetic, propionic, and butyric acids (4, 25) must first be activated to form a complex with CoA before their utilization is possible.

Protein Metabolism. Prior to utilization, proteins are hydrolyzed to their constituent amino acids. The amino acids may then be converted to keto acids by direct deamination or by transamination (69). The keto acids thus formed may combine with CoA and thus, as in the case of carbohydrates and fats, enter the tricarboxylic acid cycle. Several of the keto acids formed during the deamination process may form glycogen (6, 26, 27).

#### Ruminant Nutrition and Ketosis

Several investigations by Schambye (58, 59) in which arterial and portal blood glucose differences were measured in sheep

have shown that carbohydrate metabolism in ruminants differs from that in monogastric animals. Results of these studies indicated that little glucose is absorbed from any part of the digestive system of the sheep. These findings have been substantiated by other workers (20, 32, 45, 54, 55). Thus, monosaccharides, as such, are not a significant source of energy to the ruminant.

Holmes (30), studying the effects of administering glucose by mouth to normal cattle of all ages, found that young calves acted as monogastric animals and showed a higher and more prolonged rise in blood sugar. He likewise found the appearance of acetone bodies in the urine of adults following glucose feeding but no acetonuria in the young animals under similar conditions. This suggests a relationship between rumen function and acetone production. This worker reported anorexia, rumen atony, and diarrhea when glucose was given per os to the ruminant animal.

Formerly it was recognized that cellulose is digested with the aid of bacteria in the rumen. It has now been conclusively demonstrated that, unlike other animals, the ruminant is largely dependent upon the products of microbial fermentation and upon the micro-organisms themselves for its metabolic needs (34). The energy needs are supplied largely by short chain organic acids formed during carbohydrate fermentation (20). It has been demonstrated that these acids are absorbed directly by the rumen wall (52, 54).

Numerous investigators have shown the relationship between the rumen and rumen fermentation and ketosis (21, 22, 28, 31-34,

60, 61). It has been known for some time that the ketotic ruminant has a low blood sugar level and that intravenously administered glucose in many instances will alleviate the condition. Johnson (34), in a theoretical discussion of ruminant ketosis, pointed out that one effect of the low blood sugar values is the use of oxalacetate for the synthesis of needed glucose. As oxalacetic acid is essential in the proper functioning of the tricarboxylic acid cycle, a shortage of this substance would have far reaching effects on the metabolism of the animal. Moreover, any further oxalacetate formed during the oxidation of butyric and propionic acids could conceivably be used up rapidly in the synthesis of needed glucose. In the absence of oxalacetate, acetic acid, normally one of the principal sources of energy to the ruminant, becomes of no value. Further, it may even become a liability if it is condensed to acetoacetic acid, one of the ketone substances found to be very prevalent in ketosis. Under these circumstances body fat is utilized in an attempt to overcome the shortage of energy. This process, under the conditions shown to be present in ketosis, would result in a further build-up of ketone substances formed during fatty acid oxidation.

In most animals, when exogenous carbohydrate is lacking, proteins are broken down to supply the demand. This process of gluconeogenesis has been shown to be of little importance in the ruminant animal by McCandless and Dye (42, 43, 44). The important role played by the rumen and rumen flora has been pointed out by Underbjerg (71). It was further discussed how a dysfunction of this key organ could induce a nutritional metabolic

stress and thus lead to tissue depletion of essential metabolites. Anorexia and rumen atony have been shown to be early symptoms of ketosis in cattle. Regardless of whether they are a cause or a result of ketosis, anorexia and rumen atony would certainly decrease exogenous sources of energy. Further tissue and fat breakdown would then be required to meet energy needs and thus result in a further increase in ketone substances.

Past treatments to alleviate the condition of ketosis have been discussed by Underbjerg et al. (72). It was pointed out that these treatments are all directed at supplying glucose and/or energy either directly or indirectly. Intravenous glucose constitutes a direct way of supplying energy to the ketotic animal. Shaw et al. (66) suggested that in the treatment of ketosis with glucose, this compound should be administered periodically. Cortisone and adrenocorticotrophic hormone (ACTH) bring about gluconeogenesis whereby body protein is broken down in order to supply needed energy (63, 64). Obviously this is a biologically expensive way to supply energy to an animal whose energy metabolism is already functioning improperly. As pointed out by these and other workers sodium acetate (72), sodium propionate (60), glycerol (34, 35) and propylene glycol (35), given per os, can also be utilized for energy. After their absorption they follow the normal metabolic routes followed by short chain fatty acids.

#### MATERIALS AND METHODS

Twelve yearling Hereford heifers having an average weight

of 822 pounds were employed in this investigation. These animals were fed a balanced ration high in concentrates. The basal ration fed daily to calves 25, 29, 30, 32, 33 and 36 consisted of the following:

|   |                 |
|---|-----------------|
| Cracked yellow corn                         | 11.0 lbs        |
| Linseed meal                                | 2.5 lbs         |
| Wheat straw                                 | ad. <u>lib.</u> |
| Iodized NaCl                                | <u>20 gms</u>   |
| Calcium carbonate                           | 36.08 gms       |
| Feeding oil, containing<br>9 mg carotene/gm | 7.6 gms         |

The basal ration fed daily to calves 26, 27, 28, 31, 34 and 35 consisted of the following:

|   |                 |
|---|-----------------|
| Cracked yellow corn                         | 11.0 lbs        |
| Linseed meal                                | 2.0 lbs         |
| Alfalfa hay                                 | 2.0 lbs         |
| Wheat straw                                 | ad. <u>lib.</u> |
| Iodized NaCl                                | <u>20 gms</u>   |
| Calcium carbonate                           | 11.84 gms       |
| Feeding oil, containing<br>9 mg carotene/gm | 3.6 gms         |

Each calf was injected intravenously with glucose, fructose, and invert sugar at two week intervals. The sugars were dissolved in water to make 50 per cent solutions and were given at the rate of 0.5 gm/kg body weight. The invert sugar was prepared by mixing equal quantities of glucose and fructose so that the resulting solution contained 25 per cent glucose and 25 per cent fructose. The jugular vein was used as the injection site. Approximately five minutes were required for the administration. Blood samples were obtained from the jugular vein prior to and following the injection. The post-injection blood samples were obtained at two minutes, 30 minutes, one, two, four, and six hours following the injection. A mixture which has been shown



to stop enzymatic activity and which contained sodium fluoride, thymol, and sodium oxalate was used as the anticoagulant (37). Urine samples were collected prior to and one, two, four, and six hours following the infusions. In addition, the total urine formed and voided during the six hour post-injection period was collected from five calves in each group. Urination was induced by perineal stimulation. The blood and urine samples were refrigerated immediately upon collection and protein-free filtrates were prepared within three hours. This was done to prevent the breakdown of any glucose or fructose present in the blood or urine at the time of collection. The blood glucose was determined according to the method of Nelson (49) while blood fructose was determined by the method described by Roe et al. (57).

Duplicate glucose and fructose determinations, using an M14 Coleman spectrophotometer, were made on each blood and urine sample. Standard calibration curves for the determination of glucose and fructose are shown in Figs. 2 and 3. These curves were established prior to and checked periodically throughout the experiment. The calibrations were accomplished by using standard solutions containing known amounts of glucose and fructose.

## RESULTS AND DISCUSSION

### Blood Analysis

The blood sugar values of the 12 calves before and following the intravenous infusions are shown in Table 1. The average



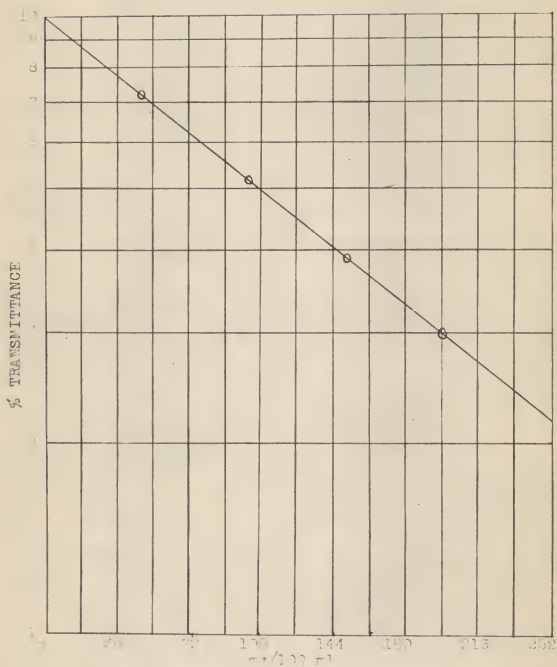


Fig. 2. Calibration curve used for the calculation of absorbance values for 0.1 ml.

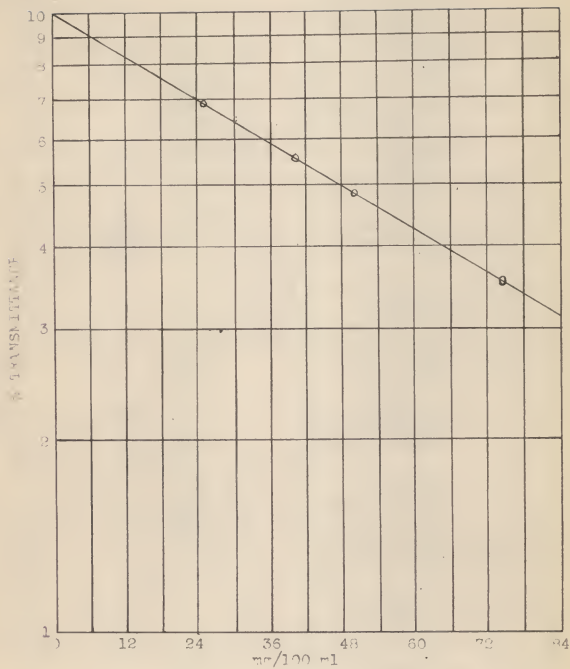


Fig. 3. Calibration curve used for the calculation of fructose values in mg/100 ml.

Table 1. Blood sugar determinations expressed in mg/100 ml following intravenous infusion of glucose at the rate of 0.5 gm/kg body weight.

| Calf    | : | Sample time |   |       |   |       |   |       |   |      |   |      |   |      |
|---------|---|-------------|---|-------|---|-------|---|-------|---|------|---|------|---|------|
| Number  | : | Pre-        | : | 2     | : | 30    | : | 1     | : | 2    | : | 4    | : | 6    |
|         | : | injection   | : | Min.: | : | Min.: | : | Hr.:  | : | Hr.: | : | Hr.: | : | Hr.: |
| 25      |   | 62          |   | 138   |   | 100   |   | 105   |   | 99   |   | -    |   | -    |
| 26      |   | 48          |   | 408   |   | 163   |   | 120   |   | 92   |   | 68   |   | 53   |
| 27      |   | 52          |   | 386   |   | 152   |   | 54    |   | -    |   | 56   |   | 57   |
| 28      |   | 56          |   | 370   |   | 178   |   | 130   |   | 88   |   | 60   |   | 62   |
| 29      |   | 53          |   | 496   |   | 146   |   | 107   |   | 60   |   | 78   |   | 50   |
| 30      |   | 55          |   | 372   |   | 220   |   | 164   |   | 144  |   | 124  |   | -    |
| 31      |   | 47          |   | 390   |   | 96    |   | 41    |   | 47   |   | 46   |   | 47   |
| 32      |   | 69          |   | 684   |   | 239   |   | 198   |   | 133  |   | 84   |   | 44   |
| 33      |   | 60          |   | 282   |   | 185   |   | 145   |   | 117  |   | 73   |   | 62   |
| 34      |   | 67          |   | 428   |   | 163   |   | 142   |   | 98   |   | 64   |   | 64   |
| 35      |   | 52          |   | 342   |   | 161   |   | 126   |   | 78   |   | 61   |   | 60   |
| 36      |   | 59          |   | 450   |   | 204   |   | 156   |   | 132  |   | -    |   | -    |
| Average |   | 56.7        |   | 395.5 |   | 166.9 |   | 123.8 |   | 98.9 |   | 71.4 |   | 55.4 |

preinjection blood sugar of the 12 calves prior to the injection of glucose was 56.7 mg/100 ml blood. The pre-injection blood sugar values ranged from 47 to 69 mg/100 ml. Following the injection of glucose the blood sugar level increased markedly with the average being 395 mg/100 ml blood at two minutes post-injection. As evidenced by this table there was considerable variation in the two minute values. This difference can be

explained by variations in injection time, by the possibility of incomplete mixing in the blood stream at two minutes, and by the variations which are found to be constant in living organisms.

After the two minute peak the blood sugar fell rapidly but in only two cases, calves 27 and 31, did it return to the pre-injection level prior to four hours. Three more of the calves, numbers 28, 34 and 35, exhibited normal blood sugar values at four hours post-injection. The remaining seven calves all showed usual blood sugar values at six hours. The most rapid fall in blood sugar in all cases occurred during the first 30 minutes as evidenced by the drop from 395 mg/100 ml at two minutes to 167 mg/100 ml at 30 minutes. Following this, the curve (Fig. 4) leveled off with normal values being assumed much more slowly.

The total blood sugar (glucose plus fructose) following the injection of fructose simulated the pattern following glucose administration (Table 2). The average pre-injection blood sugar level was 53.3 mg/100 ml blood in this instance. At two minutes post-injection the average value was 401.7 mg/100 ml blood. This figure was almost identical to the two minute average shown following glucose administration. Once more the blood sugar fell rapidly and especially during the first 30 minutes. The rate of fall once again decreased markedly after 30 minutes post-injection. In this instance calf 34 exhibited a normal blood sugar level at one hour. Calves 27, 32, 33 and 35 showed usual blood sugar values at two hours while at four hours calves 25, 26 and 29 exhibited normal readings. In three individuals a hyperglycemic condition still existed at six hours.

Table 2. Blood sugar determinations (glucose plus fructose), expressed in mg/100 ml blood, following intravenous infusion of fructose at the rate of 0.5 gm/kg body weight.

| Calf<br>Number | :    | Sample time           |                |                 |               |               |               |               |
|----------------|------|-----------------------|----------------|-----------------|---------------|---------------|---------------|---------------|
|                |      | : Pre-<br>: injection | : 2<br>: Min.: | : 30<br>: Min.: | : 1<br>: Hr.: | : 2<br>: Hr.: | : 4<br>: Hr.: | : 6<br>: Hr.: |
| 25             | -    |                       | 464            | 177             | 168           | 98            | 27            | 83            |
| 26             | 61   |                       | 412            | 148             | 113           | 74            | 54            | 59            |
| 27             | 47   |                       | 396            | 109             | 64            | 32            | 59            | 46            |
| 28             | 53   |                       | 308            | 104             | 90            | 66            | 89            | 105           |
| 29             | 52   |                       | 454            | 220             | 206           | 108           | 30            | 40            |
| 30             | 76   |                       | 534            | 162             | 112           | 76            | 104           | 79            |
| 31             | 62   |                       | 534            | 170             | 117           | 84            | 84            | -             |
| 32             | 41   |                       | 313            | 143             | 110           | 59            | 42            | -             |
| 33             | 45   |                       | 340            | 144             | 101           | 47            | 58            | 60            |
| 34             | 30   |                       | 360            | 126             | 60            | 22            | 38            | 50            |
| 35             | 43   |                       | 314            | 145             | 92            | 61            | 44            | 55            |
| 36             | 76   |                       | 392            | 142             | 122           | 80            | 116           | 56            |
| Average        | 53.3 |                       | 401.7          | 149.2           | 112.9         | 67.2          | 62.1          | 63.3          |

The average pre- and post-injection blood fructose values prior to fructose infusion are shown in Table 3. The average pre-injection level was 5.0 mg/100 ml, indicating that some in-ulooid material is normally present in bovine blood. At two minutes post-injection the blood fructose values had reached a peak of 291.7 mg/100 ml. This indicated a possible rapid conversion of fructose to glucose since the average two minute total blood

Table 3. Blood fructose determinations, expressed in mg/100 ml blood, following intravenous infusion with fructose at the rate of 0.5 gm/kg body weight.

| Calf<br>Number | :   | Sample time |        |        |       |       |       |       |
|----------------|-----|-------------|--------|--------|-------|-------|-------|-------|
|                |     | Pre-        | 2      | 30     | 1     | 2     | 4     | 6     |
|                |     | : injection | : Min. | : Min. | : Hr. | : Hr. | : Hr. | : Hr. |
| 25             | 11  | 344         | 46     | 34     | 14    | 6     | -     |       |
| 26             | 4   | 170         | 73     | 30     | 13    | 5     | 8     |       |
| 27             | 3   | 396         | 57     | 22     | 8     | 5     | 4     |       |
| 28             | 6   | 476         | 40     | 26     | 12    | 10    | 11    |       |
| 29             | 0   | 344         | 74     | 31     | 8     | 4     | 2     |       |
| 30             | 7   | 352         | 54     | 17     | 8     | 13    | 4     |       |
| 31             | 6   | 268         | 98     | 27     | 9     | 9     | 7     |       |
| 32             | 4   | 190         | 62     | 28     | 10    | 5     | -     |       |
| 33             | 3   | 270         | 74     | 39     | 10    | 8     | 5     |       |
| 34             | 6   | 304         | 64     | 22     | 9     | 7     | 6     |       |
| 35             | 3   | 216         | 53     | 24     | 6     | 4     | 5     |       |
| 36             | 7   | 170         | 56     | 36     | 22    | 21    | 4     |       |
| Average        | 5.0 | 291.7       | 62.6   | 28.0   | 10.7  | 8.1   | 5.6   |       |

sugar value following fructose administration was 401.7 mg/100 ml. The difference between these two figures, or 110 mg, would undoubtedly be true glucose. An even more rapid utilization of fructose is indicated as evidenced by the difference between the two minute and 30 minute values. At 30 minutes post-injection the average blood fructose level had dropped to 62.6 mg/100 ml blood. The blood fructose values continued to decrease although



Table 4. Blood sugar determinations (glucose plus fructose) expressed in mg/100 ml blood, following intravenous infusion with invert sugar at the rate of 0.5 gm/kg body weight.

| Calf<br>Number | : | Sample time         |             |              |            |            |            |            |
|----------------|---|---------------------|-------------|--------------|------------|------------|------------|------------|
|                |   | Pre-<br>: injection | 2<br>: Min. | 30<br>: Min. | 1<br>: Hr. | 2<br>: Hr. | 4<br>: Hr. | 6<br>: Hr. |
| 25             | : | 54                  | 402         | 175          | 146        | 96         | 40         | 55         |
| 26             | : | 36                  | 576         | 94           | 58         | 36         | 36         | 45         |
| 27             | : | 42                  | 346         | 129          | 96         | 74         | 83         | 41         |
| 28             | : | 42                  | 396         | 155          | 112        | 66         | 55         | 46         |
| 29             | : | 36                  | 382         | 121          | 68         | 25         | 32         | -          |
| 30             | : | 53                  | 332         | 133          | 113        | 75         | 63         | -          |
| 31             | : | 44                  | 360         | 110          | 47         | 44         | 53         | 52         |
| 32             | : | 43                  | 600         | 242          | 122        | 60         | 46         | 44         |
| 33             | : | 42                  | 524         | 166          | 110        | 52         | 38         | 49         |
| 34             | : | 36                  | 492         | 135          | 98         | 46         | 47         | 47         |
| 35             | : | 38                  | 456         | 133          | 86         | 41         | 49         | 47         |
| 36             | : | 35                  | 500         | 134          | 86         | 43         | 43         | 50         |
| Average        | : | 41.75               | 447         | 144          | 95         | 55         | 48.7       | 47.6       |

six hours were required for pre-injection values to be reached (Fig. 5).

The average blood sugar level in the 12 calves prior to the administration of invert sugar was 41.75 mg/100 ml blood (Table 4). This value was slightly lower than the pre-injection level previous to injection with glucose and fructose. As compared to readings following glucose and fructose injections an even

higher two minute peak was evidenced following invert sugar administration. In this instance the average two minute value was 447 mg/100 ml blood. However, the fall in blood sugar after the injection of invert sugar was more rapid as compared to glucose and fructose. There was an average decrease of 303 mg sugar/100 ml blood during the first 30 minutes post-injection. One hour following invert sugar administration the blood sugar readings of calves 26 and 31 had reached normal values. Similar levels were evidenced by seven more of the animals at two hours post-injection whereas all 12 of the calves showed normal blood sugar values at four hours. This more rapid decline in blood sugar following invert sugar infusion indicates a more rapid utilization of this carbohydrate when compared to glucose and fructose. The more rapid utilization of invert sugar could conceivably be due to the fact that fructose is more readily phosphorylated than glucose and does not require insulin for utilization (13). On the other hand, high blood fructose values apparently stimulate the production of insulin (15). Further, when invert sugar, which contains equal quantities of fructose and glucose, is infused the fructose apparently is readily phosphorylated and insulin production stimulated by both sugars thus causing a more rapid utilization of glucose.

The pre-injection blood fructose level prior to infusion with invert sugar once more showed that a small amount of inuloid material is normally present in bovine blood (Table 5). Two minute post-injection blood fructose values following the administration of a combination of glucose and fructose reached

Table 5. Blood fructose determinations, expressed in mg/100 ml blood, following intravenous infusion with invert sugar at the rate of 0.5 gm/kg body weight.

| Calf<br>Number | : | Sample time         |             |              |            |            |            |            |
|----------------|---|---------------------|-------------|--------------|------------|------------|------------|------------|
|                |   | Pre-<br>: injection | 2<br>: Min. | 30<br>: Min. | 1<br>: Hr. | 2<br>: Hr. | 4<br>: Hr. | 6<br>: Hr. |
| 25             |   | 2                   | 344         | 27           | 11         | 5          | 1          | 1          |
| 26             |   | 7                   | 256         | 28           | 14         | 9          | -          | 6          |
| 27             |   | 0                   | 236         | 22           | 8          | 4          | 2          | 2          |
| 28             |   | 0                   | 156         | 22           | 8          | 2          | 3          | 0          |
| 29             |   | 1                   | 224         | 19           | 9          | 4          | 3          | -          |
| 30             |   | 0                   | 328         | 10           | 4          | 0          | 0          | 0          |
| 31             |   | 2                   | 240         | 81           | 5          | 4          | 2          | 2          |
| 32             |   | 1                   | 532         | 6            | 1          | 1          | 1          | 1          |
| 33             |   | 3                   | 388         | 39           | 16         | 6          | 4          | 3          |
| 34             |   | 2                   | 140         | 43           | 22         | 7          | 4          | 2          |
| 35             |   | 0                   | 206         | 19           | 3          | 0          | 0          | 0          |
| 36             |   | 2                   | 360         | 26           | 13         | 7          | 4          | 2          |
| Average        |   | 1.7                 | 284.2       | 28.5         | 9.5        | 4.1        | 2.2        | 1.7        |

comparable levels to those seen after fructose infusion. However the amount of fructose found in the blood assumed readings similar to those seen prior to injection by two hours post-injection as compared to the six hours required to reach usual values following the injection of fructose alone (Fig. 5).

A summary of Tables 1, 2 and 4 showing the average total blood sugar values (glucose plus fructose) and standard deviations,

expressed as mg/100 ml blood, in 12 cattle before and following intravenous infusions of glucose, invert sugar, and fructose is shown in Table 6. These values are further depicted in Fig. 4. The average blood fructose values, expressed as mg/100 ml blood, in 12 cattle before and following intravenous injections of invert sugar and fructose are shown in Table 7. These values are depicted in Fig. 5. Typical blood sugar values, as evidenced by calf 35, following the intravenous infusion of glucose, fructose, and invert sugar are shown in Fig. 6.

#### Urine Analysis

In the glucose treated group, an average of 194.6 grams of this sugar was administered prior to the collection of all urine formed and voided during a six hour period (Table 7). Marked diuresis was evident following the injection, and particularly during the first hour post-injection. The average urinary sugar loss in the glucose injected animals was 20.76 grams. This quantity constituted a loss of 10.92 per cent of the glucose injected.

An average of 197.2 grams of fructose was administered to the five calves prior to the collection of all urine voided from the fructose treated group (Tables 9 and 11). The resulting diuresis was comparable to that seen in the glucose infused group. Twelve and one-half grams of fructose, representing a 6.3 per cent loss of this substance, were found in the six hour urine. The loss in total sugar was 16.8 grams constituting an

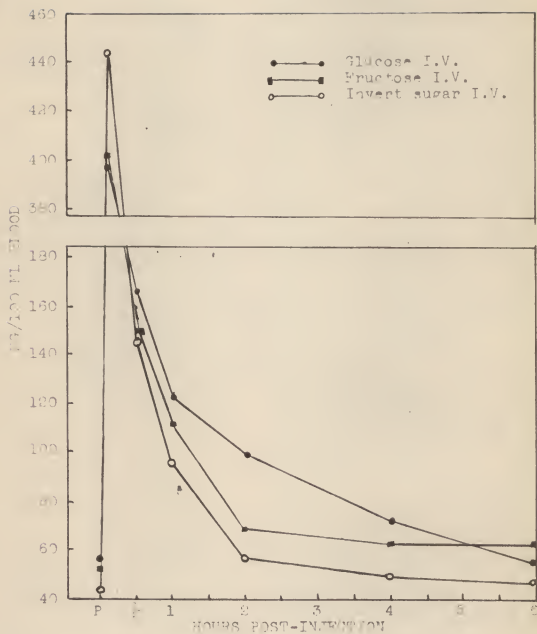


Fig. 4. Average blood sugar values of twelve calves following intravenous infusions of glucose, fructose, and invert sugar.

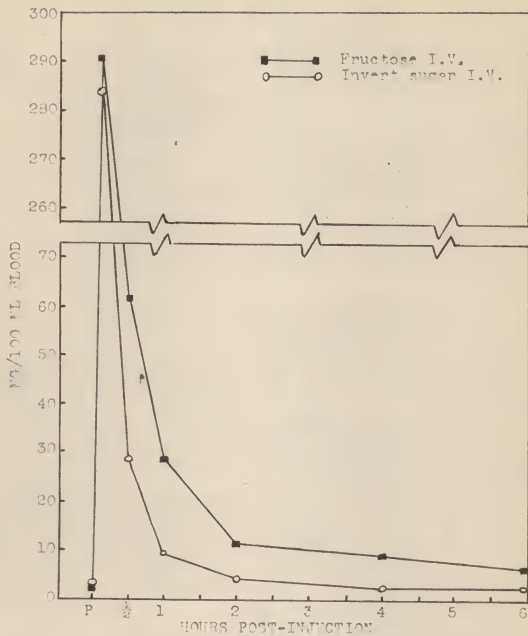


Fig. 5. Average fructose values of blood samples taken prior to and following intravenous infusions of fructose and invert sugar.



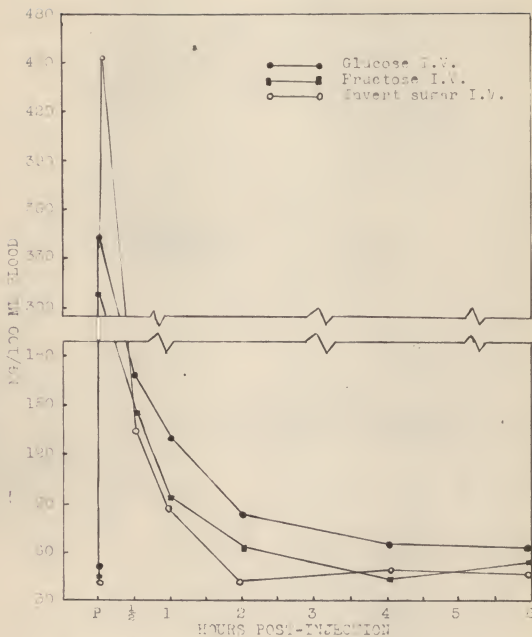


Fig. 6. Typical post-injection blood sugar values as shown by calf #35 following intravenous infusions of glucose, fructose, and invert sugar.

Table 6. Average total blood sugar values (glucose plus fructose) and standard deviations, expressed as mg/100 ml. blood, in 12 cattle before and after intravenous infusions of glucose \*, invert sugar \*, and fructose \*.

| Sample Time   | Intravenous infusion |         |              |        |          |        |
|---------------|----------------------|---------|--------------|--------|----------|--------|
|               | Glucose              |         | Invert Sugar |        | Fructose |        |
| Pre-injection | 56.7                 | ± 7.0   | 41.7         | ± 6.3  | 53.3     | ± 14.4 |
| 2 minutes     | 395.5                | ± 128.0 | 447.2        | ± 90.8 | 401.7    | ± 80.8 |
| 30 minutes    | 166.9                | ± 43.3  | 144.0        | ± 38.1 | 149.2    | ± 31.2 |
| 1 hour        | 123.8                | ± 44.4  | 95.2         | ± 28.2 | 112.9    | ± 40.6 |
| 2 hours       | 98.9                 | ± 30.7  | 55.0         | ± 20.0 | 67.2     | ± 25.2 |
| 4 hours       | 71.4                 | ± 21.5  | 48.7         | ± 13.9 | 62.1     | ± 29.4 |
| 6 hours       | 55.4                 | ± 7.3   | 47.6         | ± 4.1  | 63.3     | ± 19.8 |

\* 0.5 gm/kg body weight.

Average weight of animals - 822 lbs.

Average amount of sugar administered - 186 gm.

8.58 per cent sugar loss. Furthermore, 4.26 grams of glucose were excreted following fructose administration. This once more indicates either a possible conversion of fructose to glucose or a preferential reabsorption of fructose over glucose in the renal tubules.

Following the administration of invert sugar, diuresis was less evident than when glucose and fructose were infused separately. Of the average of 204.8 grams of invert sugar injected, 14.66 grams of sugar were found in the urine (Tables 10 and 11). This represented a 7.3 per cent sugar loss. Since the invert sugar was prepared by mixing equal quantities of fructose and

Table 7. Average blood fructose values and standard deviations, expressed as mg/100 ml blood, in 12 cattle before and after intravenous infusions of fructose and invert sugar.

| Sample Time   | Intravenous infusion |       |             |      |
|---------------|----------------------|-------|-------------|------|
|               | Invert Sugar         |       | Fructose    |      |
|               |                      |       |             |      |
| Pre-injection | 1.7 $\pm$            | 2.0   | 5.0 $\pm$   | 2.8  |
| 2 minutes     | 284.2 $\pm$          | 111.0 | 291.7 $\pm$ | 95.7 |
| 30 minutes    | 28.5 $\pm$           | 19.5  | 62.6 $\pm$  | 15.5 |
| 1 hour        | 9.5 $\pm$            | 6.1   | 28.0 $\pm$  | 6.4  |
| 2 hours       | 4.1 $\pm$            | 2.9   | 10.7 $\pm$  | 4.2  |
| 4 hours       | 2.2 $\pm$            | 1.6   | 8.1 $\pm$   | 3.8  |
| 6 hours       | 1.7 $\pm$            | 1.7   | 5.6 $\pm$   | 3.2  |

glucose, each calf received identical amounts of these two sugars during the injection of invert sugar. However, even though identical amounts were administered to the same calf in the same solution, less fructose was lost via the urine as compared to glucose. This is evidenced by the fact that following invert sugar infusion an average of 8.62 grams of glucose was found in the six hour urines as compared to 6.04 grams of fructose. This indicates either a conversion of fructose to glucose, a more rapid utilization of fructose, and/or a preferential reabsorption of fructose by the kidney tubules.

A summary of Tables 8, 9 and 10 showing the average urinary sugar excretions and standard deviations of 5 cattle following the intravenous infusions of glucose, fructose, and invert sugar

Table 8. Urinary sugar excretions in six hours following intravenous infusion with glucose at the rate of 0.5 gm/kg body weight.

| Total injection<br>and<br>Excretions | Calf number |      |      |      |      |
|--------------------------------------|-------------|------|------|------|------|
|                                      | : 26        | : 27 | : 31 | : 34 | : 35 |
| Grams glucose injected               | 195         | 164  | 193  | 219  | 202  |
| Grams glucose excreted in 6 hrs.     | 20.9        | 26.5 | 21.9 | 21.0 | 13.5 |
| Grams total sugar excreted in 6 hrs. | 20.9        | 26.5 | 21.9 | 21.0 | 13.5 |
| Ml urine excreted in 6 hrs.          | 6700        | 4675 | 4550 | 5300 | 2800 |
| Percentage sugar excreted in 6 hrs.  | 10.8        | 16.2 | 11.3 | 9.6  | 6.7  |

is shown in Table 11. These findings are depicted in Figs. 7, 8, 9 and 10.

An almost exact quantitative relationship existed between the amount of fructose excreted and the amount administered. This is evidenced by the fact that an average of 6.05 grams of fructose was eliminated following the injection of a 25 per cent solution of fructose (in invert sugar) and 12.5 grams were excreted following the injection of a 50 per cent solution of fructose (Table 8).

In contrast to these findings, Holmes (29), working with adult Ayrshire, Red Poll, and Shorthorn cattle, found that blood sugar values returned to normal within two and one-half hours following the infusion of glucose at the rate of 0.3 gm/kg body

Table 9. Urinary sugar excretions in six hours following intravenous infusion with fructose at the rate of 0.5 gm/kg body weight.

| Total injection<br>and<br>Excretions | Calf number |      |      |      |      |
|--------------------------------------|-------------|------|------|------|------|
|                                      | : 26        | : 27 | : 28 | : 31 | : 33 |
| Grams fructose injected              | 172         | 187  | 227  | 216  | 184  |
| Grams glucose excreted in 6 hrs.     | 4.0         | 4.6  | 4.5  | 2.7  | 5.5  |
| Grams fructose excreted in 6 hrs.    | 12.0        | 8.9  | 19.9 | 9.6  | 12.1 |
| Grams total sugar excreted in 6 hrs. | 16.00       | 13.5 | 24.5 | 12.4 | 17.6 |
| Ml urine excreted in 6 hrs.          | 3750        | 5920 | 5525 | 3950 | 3800 |
| Percentage sugar excreted in 6 hrs.  | 9.3         | 7.3  | 10.6 | 5.9  | 9.6  |

weight. Two to three minutes were required for this infusion. He reported the amount of sugar excreted in the urine under these conditions varied from 2.6 percent to 20.5 percent of the quantity given. The average quantity excreted was 10.3 percent. Bell and Jones (3), working with cross-bred adult Ankole and Zebu males and non-gravid heifers, injected glucose intravenously in varying amounts. Fifty percent solutions of glucose were injected at the rate of 20 ml/minute. Under these conditions it was found that 0.05 gm glucose/kg body weight was the largest amount of this sugar that could be infused in which no glycosuria occurred. When glucose was infused at rates of 0.1, 0.2

Table 10. Urinary sugar excretions in six hours following intravenous infusion with invert sugar at the rate of 0.5 gm/kg body weight.

| Total injection<br>and<br>Excretions     | Calf number |      |      |      |      |
|--|-------------|------|------|------|------|
|  | : 25        | : 28 | : 29 | : 33 | : 35 |
| Grams invert<br>sugar injected           | 212         | 202  | 222  | 208  | 180  |
| Grams glucose ex-<br>creted in 6 hrs.    | 8.6         | 16.4 | 4.8  | 4.6  | 8.7  |
| Grams fructose ex-<br>creted in 6 hrs.   | 3.3         | 6.1  | 3.4  | 6.3  | 11.1 |
| Grams total sugar<br>excreted in 6 hrs.  | 11.9        | 22.5 | 8.2  | 10.9 | 19.8 |
| Ml urine excreted<br>in 6 hrs.           | 4850        | 1880 | 1975 | 3840 | 3510 |
| Percentage sugar ex-<br>creted in 6 hrs. | 5.6         | 11.1 | 3.7  | 5.2  | 10.9 |

and 0.5 gm/kg, these workers reported normal blood sugar values at two hours following glucose infusion with a renal threshold of 98 mg/100 ml blood. Although no attempt was made to determine the renal threshold for glucose in the present study, this reported value would seem to agree with the findings presented. This is supported by the decrease in the quantity of glucose and fructose (Tables 12 and 13) found in the urine as blood sugar values decreased. These urinary sugar values are depicted in Figs. 11 and 12.



Table 11. Average urinary sugar excretions and standard deviations of 5 cattle following intravenous infusions of glucose, invert sugar, and fructose.

| Total Injection<br>and<br>Excretions | Intravenous Infusion |                  |                  |
|--------------------------------------|----------------------|------------------|------------------|
|                                      | Glucose              | Invert Sugar     | Fructose         |
| Grams sugar injected.*               | 194.6 $\pm$ 19.9     | 204.8 $\pm$ 14.3 | 197.2 $\pm$ 23.2 |
| Grams glucose excreted in 6 hrs.     | 20.8 $\pm$ 4.7       | 8.6 $\pm$ 4.77   | 4.3 $\pm$ 1.0    |
| Grams fructose excreted in 6 hrs.    | 0                    | 6.1 $\pm$ 3.2    | 12.5 $\pm$ 4.4   |
| Grams total sugar excreted in 6 hrs. | 20.8 $\pm$ 4.7       | 14.7 $\pm$ 6.2   | 16.8 $\pm$ 4.8   |
| Ml urine excreted in 6 hrs.          | 4805 $\pm$ 1409      | 3211 $\pm$ 1272  | 4599 $\pm$ 1047  |
| Percent sugar excreted in 6 hrs.     | 10.9 $\pm$ 3.8       | 7.3 $\pm$ 3.5    | 8.5 $\pm$ 2.0    |

\* 0.5 gm/kg body weight.

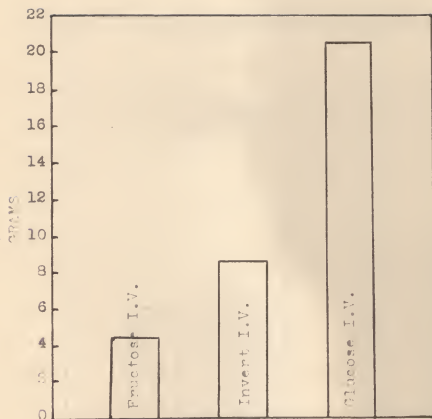


Fig. 7. Average urinary glucose eliminated by five calves in six hours following intravenous infusions of glucose, fructose, and invert sugar.

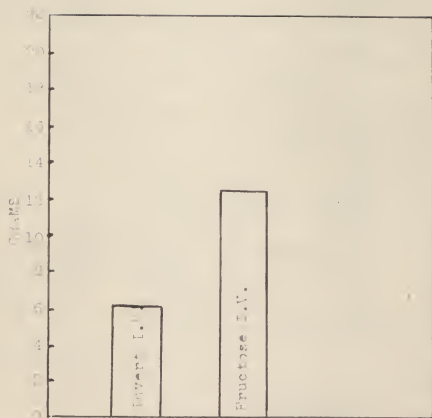


Fig. 9. Average primary fructose eliminated by five calves following intravenous infusions of fructose and invert sugar.

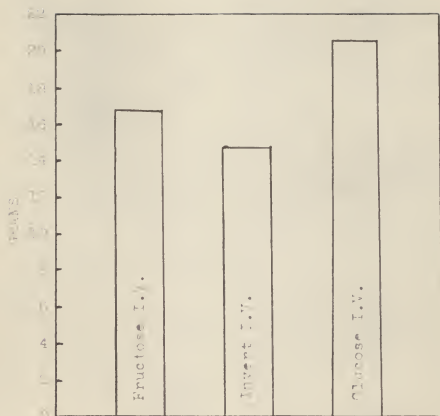


Fig. 9. Average urinary sugar eliminated by six calves in six hours following intravenous infusions of glucose, fructose, and invert sugar.

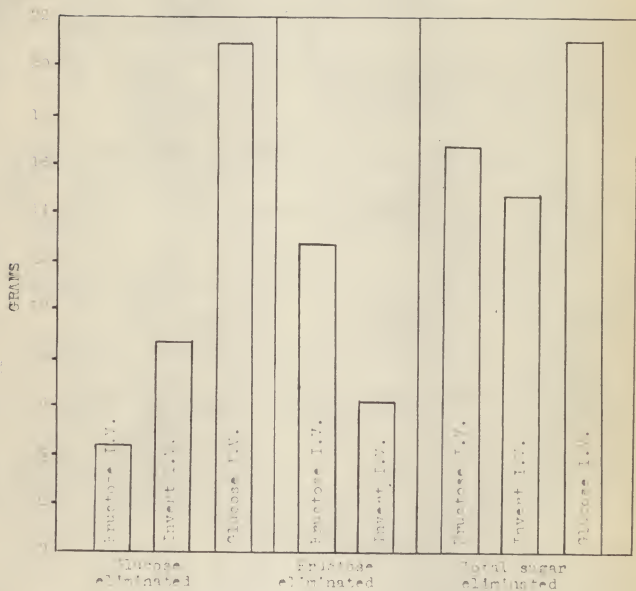


Fig. 10. Average urinary glucose, fructose, and total sugar excreted by five calves in six hours following intravenous infusions of glucose, fructose, and latent sugar.

Table 12. Average urinary sugar, expressed in mg/100 ml urine, in 10 cattle before and after intravenous infusions of glucose, fructose, and invert sugar.

| Sample        | Intravenous infusion |              |          |
|---------------|----------------------|--------------|----------|
| Time          | Glucose              | Invert Sugar | Fructose |
| Pre-injection | 0                    | 0            | 0        |
| 1 hour        | 1099                 | 236          | 467      |
| 2 hours       | 921                  | 46           | 303      |
| 4 hours       | 663                  | 74           | 213      |
| 6 hours       | 104                  | 51           | 158      |

Table 13. Average urinary fructose, expressed in mg/100 ml urine, in 10 cattle before and after intravenous infusions of fructose and invert sugar.

| Sample        | Intravenous infusion |              |
|---------------|----------------------|--------------|
| Time          | Fructose             | Invert Sugar |
| Pre-injection | 0                    | 0            |
| 1 hour        | 329                  | 141          |
| 2 hours       | 150                  | 29           |
| 4 hours       | 46                   | 23           |
| 6 hours       | 27                   | 10           |



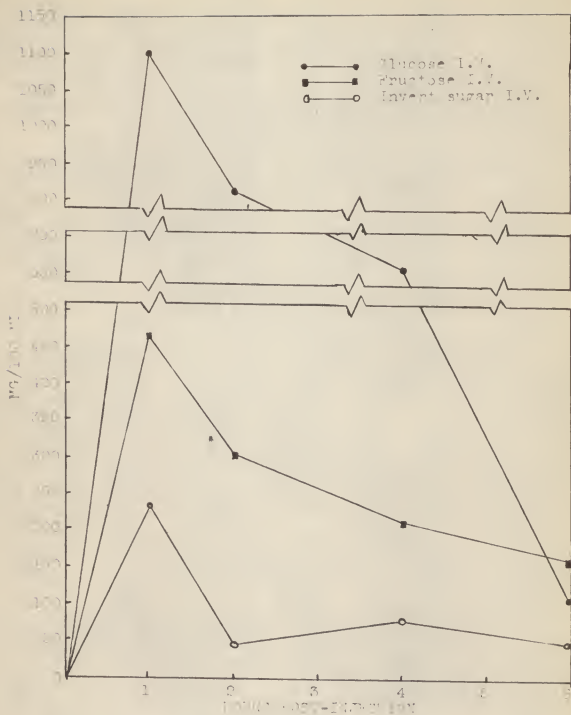


FIG. 11. Average total sugar values of urine samples taken one, two, four, and six hours following intravenous infusions of glucose, fructose, and invert sugar.

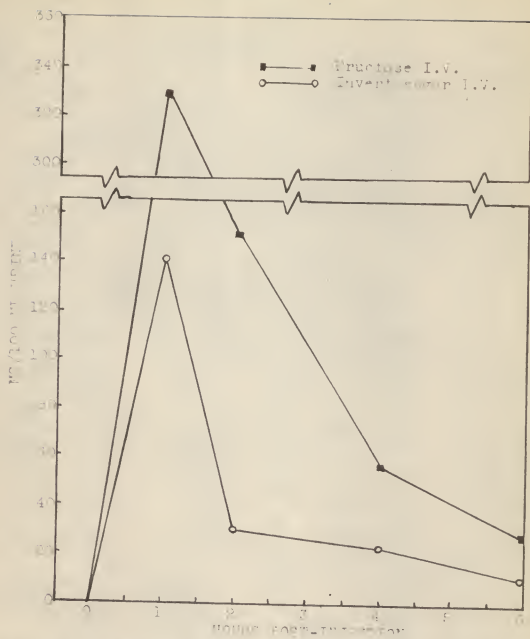


FIG. 12. Average fructose values of whole samples taken one, two, four, and six hours following intravenous injections of fructose and invert sugar.

## SUMMARY AND CONCLUSIONS

1. Twelve yearling Hereford heifers were infused intravenously with equal quantities of glucose, fructose, and invert sugar at two week intervals. Blood and urine samples were collected prior to and at periodic intervals following the administration of the sugars.

2. The average blood sugar value prior to glucose injection was 56.7 mg/100 ml blood. Following the infusion the blood sugar level increased markedly and reached an average peak of 395 mg/100 ml blood. After the two minute high the blood sugar level fell rapidly but in only two cases did it return to the pre-injection levels prior to four hours and in eight of the twelve calves it required six hours for normal values to be attained.

3. The total blood sugar (glucose plus fructose) following the injection of fructose simulated the pattern shown following glucose administration. However, following fructose infusion the blood sugar values of five of the calves returned to readings within the normal range at two hours and all except three had reached the usual value at four hours post-injection.

4. When invert sugar was infused, the total blood sugar reached even higher two minute post-injection levels than when either glucose or fructose was injected separately. Following the high two minute peak the blood sugar values returned to normal levels more rapidly when compared with either fructose or glucose administration. In nine calves the values were within

the normal range at the two hour post-injection interval and all readings were normal at four hours.

5. Diuresis was marked in the calves receiving glucose and fructose but was less evident following invert sugar administration. The average urinary sugar losses expressed in per cent were 10.6, 8.5, and 7.1 following the infusion of glucose, fructose, and invert sugar, respectively. This trend was evident throughout the investigation although the high standard deviations prevented any statistical significance.

6. The results presented indicate that in the normal bovine, as in monogastric animals, intravenously administered fructose and invert sugar are more readily utilized than glucose. Further, less urinary sugar loss was found following the injection of these two sugars and especially after invert sugar. The superiority described of fructose and invert sugar in the normal animal lends support to a possible marked advantage of fructose and/or invert sugar in the treatment of cattle with ketosis.

## ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to his major professor, Dr. G. K. L. Underbjerg, for his guidance in carrying out this investigation as well as in the preparation of this thesis. The author is also indebted to Dr. M. J. Swenson for his material assistance in completing this work and his interest in the preparation of this thesis.

## REFERENCES

1. Baker, N., I. L. Chaikoff, and A. Schusdek.  
Effect of fructose on lipogenesis from lactate and acetate in the diabetic liver. *Jour. Biol. Chem.* 194:435-443. 1952.
2. Beal, J. M., J. L. Smith, and P. M. Frost.  
Surgery. 33:721. 1953. Original not seen. *From Nutr. Rev.* 11:299-301. 1953.
3. Bell, F. R., and E. R. Jones.  
Glucose tolerance in the bovine. *Jour. Comp. Path. and Ther.* 55:117-124. 1945.
4. Block, K.  
Interrelationships of lipid and carbohydrate metabolism. *Ann. Rev. Biochem.* 21:273-300. 1952.
5. Brady, R. O., and S. Gurin.  
Biosynthesis of labeled fatty acids and cholesterol in experimental diabetes. *Jour. Biol. Chem.* 187:589-596. 1950.
6. Butts, J. S., H. Blunden, and M. Dunn.  
Studies in amino acid metabolism: III The fate of dl-leucine, dl-norleucine, and dl-isoleucine in the normal animal. *Jour. Biol. Chem.* 120:289-295. 1937.
7. Chambers, W. H.  
Undernutrition and carbohydrate metabolism. *Physiol. Rev.* 18:248-296. 1938.
8. Chernick, S. S., and I. L. Chaikoff.  
Two blocks in the carbohydrate utilization in the liver of the diabetic rat. *Jour. Biol. Chem.* 188:389-396. 1951.
9. Chernick, S. S., and I. L. Chaikoff.  
Insulin and hepatic utilization of glucose for lipogenesis. *Jour. Biol. Chem.* 186:535-542. 1950.
10. Chernick, S. S., E. J. Masoro, and I. L. Chaikoff.  
The in vitro conversion of  $C^{14}$  labeled glucose to fatty acids. *Proc. Soc. Exp. Biol. and Med.* 73:348-352. 1950.
11. Chernick, S. S., I. L. Chaikoff, E. J. Masoro, and E. Isaef. <sup>1</sup>  
Lipogenesis and glucose oxidation in the liver of the alloxan-diabetic rat. *Jour. Biol. Chem.* 186:527-534. 1950.



12. Cori, C. F.  
The fate of sugar in the animal body: III The rate of glycogen formation in the liver of normal and insulinized rats during the absorption of glucose, fructose, and galactose. Jour. Biol. Chem. 70:577-585. 1926.
13. Cori, C. F., and G. T. Cori.  
The fate of sugar in the animal body: IV The tolerance of normal and insulinized rats for intravenously injected glucose and fructose. Jour. Biol. Chem. 72:597-614. 1927.
14. Cross, R. J., J. V. Taggart, G. A. Covo, and D. E. Green.  
Studies on the cyclophorase system: VI The coupling of oxidation and phosphorylation. Jour. Biol. Chem. 177: 655-678. 1949.
15. Davidson, J. N., W. O. Kermack, D. M. Mowat, and C. P. Stewart.  
Fructose metabolism in the intact animal. Biochem. Jour. 30:433-441. 1936.
16. Deuel, H. J.  
The intermediary metabolism of fructose and galactose. Physiol. Rev. 16:173-215. 1936.
17. Doershuk, A. P.  
Some studies on the metabolism of glycerol-1-C<sup>14</sup>. Jour. Biol. Chem. 193:39-40. 1951.
18. Doershuk, A. P.  
Mechanism studies of glycogen and glyceride glycerol biosynthesis. Jour. Biol. Chem 196:423-426. 1952.
19. Drucker, W. R.  
Surgical Forum of the American College of Surgeons.  
Philadelphia: W. E. Saunders, 1952. 543 p. Original not seen. From Nutr. Rev. 12:63. 1954.
20. Dukes, H. H.  
The Physiology of Domestic Animals. 6th ed. Ithaca, N.Y.: Comstock, 1947.
21. Dye, J. A., and E. J. McCandless.  
A physiological approach to the problem of ketosis: I Basic features of the metabolic processes concerned in ketosis. Cornell Vet. 38:331-340. 1948.
22. Elsdon, S. R., and A. T. Phillipson.  
Ruminant digestion. Ann. Rev. Biochem. 17:705-726. 1948.

23. Felts, J. M., I. J. Chalkoff, and M. J. Osborn.  
Insulin and the fate of lactate in the diabetic liver.  
Jour. Biol. Chem. 191:683-692. 1951.
24. Frost, D. V., J. P. Miller, and R. K. Richards.  
Utilization of invert sugar as compared with dextrose.  
Jour. Appl. Physiol. 4:793-796. 1952.
25. Green, D. E.  
Integrated enzyme activity in soluble extracts of heart  
muscle. Science. 115:661-665. 1952.
26. Hess, W. C.  
The rates of absorption and the formation of liver gly-  
cogen by methionine, cystine and cysteine. Jour. Biol.  
Chem. 181:23-30. 1949.
27. Hess, W. C.  
The rates of absorption and the formation of liver gly-  
cogen by DL-threonine. Jour. Am. Chem. Soc. 72:1407.  
1950.
28. Hoflund, S., and H. Hedstrom.  
Disturbances in rumen digestion as a predisposing fac-  
tor in the appearance of acetoneamia. Cornell Vet. 38:  
405-417. 1948.
29. Holmes, J. R.  
Carbohydrate metabolism in the bovine. Jour. Comp. Path.  
and Ther. 61:1-14. 1951.
30. Holmes, J. R.  
Carbohydrate metabolism in the bovine: III The effects  
of the administration of glucose by mouth to normal  
cattle of various ages. Jour. Comp. Path. and Ther. 62:  
41-53. 1952.
31. Jarrett, I. G., and B. J. Potter.  
Metabolism of acetate and propionate in the ruminant.  
Nature. 116:515-517. 1950.
32. Johnson, R. B.  
The relative rates of absorption of the volatile acids  
from the rumen and their relationship to ketosis.  
Cornell Vet. 41:115-121. 1951.
33. Johnson, R. B.  
New methods of treating ketosis. A preliminary report.  
North Am. Vet. 32:327-332. 1951.
34. Johnson, R. B.  
A theoretical discussion of ruminant ketosis. Am. Jour.  
Vet. Res. 14:366-375. 1953.

35. Johnson, R. B.  
The treatment of ketosis with glycerol and propylene glycol. Cornell Vet. 44:6-21. 1954.
36. Lehninger, A. L.  
From fats to energy. Jour. Ag. and Food Chem. 1:1194-1198. 1953.
37. Levinson, S. A., and R. P. MacFate.  
Clinical Laboratory Diagnosis. 2d ed. Philadelphia: Lea and Febiger, 1943.
38. Lipmann, F.  
Development of the acetylation problem, a personal account. Science. 120:855-865. 1954.
39. Littlefield, J. W., and D. R. Sanadi.  
Role of co-enzyme A and diphosphopyridine nucleotide in the oxidation of pyruvate. Jour. Biol. Chem. 199:65-70. 1952.
40. Mackler, B., H. Lichtenstein, and G. M. Guest.  
Effects of ammonium chloride acidosis on glucose tolerance in dogs. Am. Jour. Physiol. 168:126-130. 1952.
41. Mackler, B., J. Mithosfer, H. Graubarth, P. Ammentorp, and G. M. Guest.  
Glucose utilization in acidotic hepatectomized dogs and eviscerated dogs. Am. Jour. Physiol. 169:561-564. 1952.
42. McCandless, E. L., and J. A. Dye.  
Effects of alloxan administration in the calf. Am. Jour. Physiol. 156:355-360. 1949.
43. McCandless, E. L., and J. A. Dye.  
Physiological changes in intermediary metabolism of various species of ruminants incident to functional development of the rumen. Am. Jour. Physiol. 162:434-446. 1950.
44. McCandless, E. L., B. A. Woodward, and J. A. Dye.  
Alloxan diabetes in sheep under fasting and non-fasting conditions. Am. Jour. Physiol. 154:94-106. 1948.
45. McClymont, G. L.  
Identification of the volatile fatty acid in peripheral blood and rumen of cattle and the blood of other species. Austral. Jour. Agr. Res. 2:92-103. 1951. Original not seen. From Am. Jour. Vet. Res. 14:366-375. 1953.



46. Miller, K., W. R. Drucker, J. E. Owens, J. W. Craig, and H. Woodward, Jr.  
Metabolism of intravenous fructose and glucose in normal and diabetic subjects. Jour. Clin. Invest. 31:115-125. 1952.
47. Minkowski, O.  
Untersuchungen über den diabetes mellitus nach exstirpation des pankreas. Archiv. f. experiment. Pathol. u. Pharmacol. 31:85-189. 1893.
48. Moncrief, J. A., K. B. Coldwarter, and R. Elman.  
Arch. Surg. 67:57. 1953. Original not seen. From Nutr. Rev. 12:63. 1954.
49. Nelson, H.  
A photometric adaptation of the Somogi Method for the determination of glucose. Jour. Biol. Chem. 153:375-380. 1944.
50. Ochoa, S.  
Biological mechanisms of carboxylation and decarboxylation. Physiol. Rev. 31:56-106. 1951.
51. Ochoa, S., and J. R. Stern.  
Carbohydrate metabolism. Ann. Rev. Biochem. 21:547-602. 1952.
52. Osborn, M. J., I. L. Chaikoff, and J. M. Felts.  
Insulin and the fate of pyruvate in the diabetic liver. Jour. Biol. Chem. 193:549-555. 1951.
53. Pfander, W. H., and A. T. Phillipson.  
The rates of absorption of acetic, propionic, and n-butyric acids. Jour. Physiol. 122:102-110. 1953.
54. Phillipson, A. T.  
Fermentation in the alimentary tract and the metabolism of the derived fatty acids. Nutr. Abstr. Rev. 17:12-18. 1947.
55. Phillipson, A. T. and R. A. McAnally.  
Studies on the fate of carbohydrates in the rumen of sheep. Jour. Exp. Biol. 19:199-214. 1942.
56. Rice, C. O., and J. H. Strickland.  
Parenteral nutrition in the surgical patient. Jour. Indiana State Med. Assn. 45:122-130. 1952. Original not seen. From Nutr. Rev. 12:63. 1954.
57. Roe, J. H., J. H. Epstein, and N. P. Goldstein.  
A photometric method for the determination of inulin in plasma and urine. Jour. Biol. Chem. 173:839-845. 1949.

58. Schambye, P.  
Volatile acids and glucose in portal blood of sheep.  
Vet. Med. 3:555-574. 1951.
59. Schambye, P.  
Volatile acids and glucose in portal blood of sheep: III  
The influence of orally administered glucose. Vet. Med.  
3:1003-1004. 1951.
60. Schultz, L. H.  
Treatment of ketosis in dairy cattle with sodium propionate. Cornell Vet. 42:143-155. 1952.
61. Schultz, L. H., and V. R. Smith.  
Experimental alteration of the sugar and ketone levels  
of the blood of ruminants in relation to ketosis. Jour.  
Dai. Sci. 34:1191-1199. 1951.
62. Seekles, L.  
A note on the treatment of ketosis in milk cows with  
ammonium lactate. Am. Jour. Vet. Res. 63:494. 1951.
63. Shaw, J. C.  
Studies on ketosis in dairy cattle: IX Therapeutic  
effect of adrenal cortical extracts. Jour. Dai. Sci.  
30:307-311. 1947.
64. Shaw, J. C., B. C. Hatzitolos, and A. C. Chung.  
Studies on ketosis in dairy cattle: XV Response to  
treatment with cortisone and ACTH. Science 114:574-576.  
1951.
65. Shaw, J. C., and C. P. Ross.  
Glucose therapy in ketosis in cattle. Jour. Dai. Sci.  
24:503-504. 1941.
66. Shaw, J. C., R. C. Powell, and G. C. White.  
Studies on ketosis in dairy cattle: IV The effect of  
glucose therapy and pasture feeding in cases of clinical  
ketosis. Jour. Am. Vet. Med. Assoc. 100:473-478. 1942.
67. Smith, L. H., R. H. Ettinger, and D. Seligson.  
A comparison of the metabolism of fructose and glucose in  
hepatic disease and diabetes mellitus. Jour. Clin.  
Invest. 32:273-282. 1953.
68. Smith, J. L., J. M. Beal, and P. Frost.  
Surgery. 31:720. 1952. Original not seen. From Nutr.  
Rev. 11:299-301. 1953.
69. Tarver, H.  
Metabolism of amino acids and proteins. Ann. Rev. Biochem. 21:301-332. 1952.



70. Thin, C., and A. Robertshaw.  
Biochemical aspects of ruminant ketosis. Jour. Comp.  
Path. and Ther. 63:184-194. 1953.
71. Underbjerg, G. K. L.  
Ketosis and carbohydrate metabolism in the bovine. Iowa  
Vet. 25:9-24. 1954.
72. Underbjerg, G. K. L., D. D. Goetsch, and M. J. Swenson.  
Treatment of ketosis. Iowa Vet. 25:26-27. 1954.
73. Van Itallie, T. B., M. C. Morgan, R. T. Cathcart,  
G. G. Leduc, and L. B. Dotti.  
Peripheral assimilation of fructose in man. Proc. Soc.  
Exp. Biol. and Med. 83:713-715. 1953.
74. Vestling, C. S., A. K. Mylrois, U. Irish, and N. H. Grant.  
Rat liver fructokinase. Jour. Biol. Chem. 185:789-801.  
1950.
75. Weichselbaum, T. E., R. Elman, and R. H. Lund.  
Comparative utilization of fructose and glucose given  
intravenously. Proc. Soc. Exp. Biol. Med. 75:816-818.  
1950.
76. Weinstein, J. J.  
Ann. Western Med. Surg. 373:179. 1950. Original not  
seen. From Nutr. Rev. 9:173. 1951.
77. Weinstein, J. J.  
Carbohydrate therapy: Use of invert sugar in non-  
diabetics. Med. Ann. Dist. Columbia 20:355-359. 1951.  
Original not seen. From Nutr. Rev. 9:173. 1951.
78. Whittlesey, P., and C. G. Zubrod.  
The effect of intravenously administered fructose on  
the ketone bodies of the depancreatized dog. Jour.  
Pharm. and Exp. Ther. 110:226-231. 1954.
79. Wierzechowski, M.  
Intermediary carbohydrate metabolism: I Influence of  
insulin on levulose and glucose intravenously adminis-  
tered. Jour. Biol. Chem. 68:631-652. 1926.
80. Winslow, S. R.  
Surgery. 4:867. 1938. Original not seen. From Nutr.  
Rev. 9:173. 1951.
81. Woodyatt, R. T., W. D. Sansum, and R. M. Wilder.  
Prolonged and accurately timed intravenous injections  
of sugar. Jour. Am. Med. Assoc. 65:2067-2070. 1915.



82. Wyshak, G. H., and I. L. Chaikoff.

Metabolic defects in the liver of fasted rats as shown  
by utilization of  $C^{14}$  labeled glucose and fructose.

Jour. Biol. Chem. 200:851-857. 1953.

THE UTILIZATION OF INTRAVENOUSLY ADMINISTERED  
GLUCOSE, FRUCTOSE, AND INVERT SUGAR IN CATTLE

by

DENNIS DONALD GOETSCH

B. S., Kansas State College  
of Agriculture and Applied Science, 1952  
D. V. M., Kansas State College  
of Agriculture and Applied Science, 1952

AN ABSTRACT OF A THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Physiology

KANSAS STATE COLLEGE  
OF AGRICULTURE AND APPLIED SCIENCE

1955

## ABSTRACT

The demonstration that insulin affected phosphorylation of glucose and that specific hexokinases for fructose and glucose existed in the liver and muscles led to investigations with fructose as a therapeutic agent in diabetes mellitus and other disturbances in carbohydrate metabolism. Later studies indicated separate metabolic pathways for glucose and fructose and that fructose metabolism was not affected in diabetes. Further investigations showed that the utilization of fructose was not dependent on insulin and that fructose was more easily phosphorylated than glucose. Other workers have demonstrated less urinary loss from intravenously administered fructose and invert sugar as compared to glucose. Direct assimilation of fructose by peripheral tissues has likewise been demonstrated. Other investigations have indicated that the rate of disappearance of glucose from the blood is slower in acidotic animals than in the normal. Thus acidosis inhibited cellular uptake of glucose and/or processes of phosphorylation. Recent work has demonstrated that fructose is ketolytic in depancreatized, ketotic dogs.

These findings suggested an evaluation of the utilization of fructose and invert sugar in cattle since it is well known that ruminants differ markedly in their carbohydrate metabolism from that of monogastric animals. Further, in case of greater advantages of these sugars over glucose, their superiority as valuable therapeutic agents would be indicated in the many disturbances of ruminants where therapy with glucose is employed and especially

in ketosis of dairy cattle.

Twelve yearling Hereford heifers fed a basal ration of cracked corn, linseed oil meal, wheat straw, salt, and vitamin A feeding oil were used in this investigation. Each calf was injected intravenously with glucose, fructose, and invert sugar in 50 per cent solutions at the rate of 0.5 gm/kg body weight at two week intervals. The invert sugar was prepared by mixing equal quantities of glucose and fructose so that the resulting solution contained 25 per cent glucose and 25 per cent fructose. The jugular vein was used as the injection site. The time required for the injection was approximately five minutes. Blood samples were obtained from the jugular vein prior to and at periodic intervals following the infusion. The post-injection samples were taken at two minutes, 30 minutes, one, two, four, and six hours following the injection. A fluoride-oxalate-thymol mixture was used as the anti-coagulant.

Urine samples were collected prior to and one, two, four, and six hours following the injection. In addition the total urine formed and voided in six hours after the infusion was collected from five calves in each group. The blood and urine samples were refrigerated immediately upon collection and protein-free filtrates prepared within three hours.

The average blood sugar value prior to glucose injection was 56.7 mg/100 ml blood. Following the infusion the blood sugar level increased markedly and reached an average peak of 395 mg/100 ml blood. After the two minute high the blood sugar level fell rapidly but in only two cases did it return to the

pre-injection levels prior to four hours and in eight of the twelve calves it required six hours for normal values to be attained.

The total blood sugar (glucose plus fructose) following the injection of fructose simulated the pattern shown following glucose administration. However, following fructose infusion the blood sugar values of five of the calves returned to readings within the normal range at two hours and all except three had reached the usual value at four hours post-injection.

When invert sugar was infused the total blood sugar reached even higher two minute post-injection levels than when either glucose or fructose was injected separately. Following the high two minute peak the blood sugar values returned to normal levels more rapidly when compared with either fructose or glucose administration. In nine calves the values were within the normal range at the two hour post-injection interval and all readings were normal at four hours.

Diuresis was marked in the calves receiving glucose and fructose but was less evident following invert sugar administration. The average urinary sugar losses expressed in per cent were 10.6, 8.5, and 7.1 following the infusion of glucose, fructose, and invert sugar, respectively. This trend was evident throughout the investigation although the high standard deviations prevented any statistical significance.

The results presented indicate that in the normal bovine, as in monogastric animals, intravenously administered fructose and invert sugar are more readily utilized than glucose. Further,

less urinary sugar loss was found following the injection of fructose and invert sugar. The superiority described of fructose and invert sugar in the normal animal lends support to a possible marked advantage of fructose and/or invert sugar in the treatment of cattle with ketosis.

